Allosteric Inhibition of Ubiquitin-like Modifications by a Class of Inhibitor of SUMO-Activating Enzyme.

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Public Summary:
Small ubiquitin-like modifier (SUMO)-activating enzyme (E1) has been shown previously as a target to eradiate cancer stem cells of various cancer types. In this study, we discovered a novel mechanism to inhibit this target through a previously unknown site of the enzyme resulting in a major change of the shape of the enzyme to destroy its catalytic activity. Targeting this site not only destroys the enzyme activity of the SUMO E1, but also enhances its degradation in vivo, presumably due to a conformational change induced by the compound. The mechanism we identified is applicable to other family members of this class of enzymes and will spur new innovation in therapeutic discovery targeting new signaling pathways that cancer stem cell relies on.

Scientific Abstract:
Ubiquitin-like (Ubl) post-translational modifications are potential targets for therapeutics. However, the only known mechanism for inhibiting a Ubl-activating enzyme is through targeting its ATP-binding site. Here we identify an allosteric inhibitory site in the small ubiquitin-like modifier (SUMO)-activating enzyme (E1). This site was unexpected because both it and analogous sites are deeply buried in all previously solved structures of E1s of ubiquitin-like modifiers (Ubl). The inhibitor not only suppresses SUMO E1 activity, but also enhances its degradation in vivo, presumably due to a conformational change induced by the compound. In addition, the lead compound increased the expression of miR-34b and reduced c-Myc levels in lymphoma and colorectal cancer cell lines and a colorectal cancer xenograft mouse model. Identification of this first-in-class inhibitor of SUMO E1 is a major advance in modulating Ubl modifications for therapeutic aims.